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Modelling Influenza Vaccination Outcomes

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ABSTRACT

Modelling response to influenza vaccination can improve our understanding of how proposed factors, older age, past exposure to influenza viruses, and health disorders, used together, affect antibody production after influenza vaccination. Knowledge about this may be important when planning influenza vaccination protocols. This problem will be emphasized especially in the future, when many alternative vaccines and vaccination approaches are likely to be allowed for a routine use. A major difficulty, in modelling response to influenza vaccination, is how to identify health parameters, suitable for general use. To deal with the complexity of this task, we reached out for the concept of a systems biology and machine learning methods. Based on this approach, we showed that it is possible to construct useful models of influenza vaccination outcomes. In addition, by varying criteria for definition of the model's outcome measure, that is, of low antibody response to influenza vaccination, we showed that a set of health parameters, albeit limited, are necessary for model to achieve a wider practical use.

Keywords: Influenza Vaccination Outcome; Modeling; The Health-Status; Systems Biology; Logistic Regression; Vaccination Protocols

1. Introduction

Current approach for the prevention and control of influenza epidemics is annual vaccination with a trivalent inactivated influenza vaccine [1]. This procedure is advised primarily to subjects at higher risk for influenza-related complications and deaths, such as elderly (≥65y) and patients with chronic health conditions [2,3]. The problem is that influenza vaccines are, in general, less effective in elderly, than in younger population groups [4]. While, for example, protective postvaccination antibody titres can be found in 70% - 90% of healthy adults, these results are much worsen in elderly, achieving the protection-rate of 40% - 60% [5,6].

In order to improve the efficacy of influenza vaccination in high risk groups, new vaccines and vaccination approaches are now being pursued [7]. This imposes on primary care workers a task of making a decision of who should be a candidate for an alternative vaccine approach and who should not. The problem is especially emphasized because of the inconsistency of the reports on the outcomes of influenza vaccination campaigns. In contrast to what may be expected, some reports indicate that the influenza vaccination in high risk groups are as effective as in the young control groups [8]. Or, there are reports showing that, even within the same high risk group, individuals differ with each other in postvaccination antibody responses [9]. In elderly population, benefits from influenza vaccination of healthy people, in contrast to ill ones, have not yet been proved [10].

Evidence-based-medicine relies on the conventional, reductionist methods, and can not provide evidence to guide a decision-making, as decisions in this area are likely to deal with a complex problem-solving [11]. This is due to the fact that multiple factors, including older age, chronic diseases and past exposure to influenza viruses (the number of previous vaccinations and pree-xisting antibody titres), have been identified as possible causes for differences in immune response to influenza vaccination [12,13]. Moreover, in relation to chronic diseases, it has been showed that different stages of a disease, co-morbidity, lifestyle factors, or particular biochemical disorders, may all contribute to the postvaccination antibody response, adding to the complexity of the task [9,14,15]. As a methodology approach, to support a decision-making, we suggest the use of a computer-based modelling [16]. Similar attempts, by using multivariate analysis to assess the association of potentially relevant factors with post-vaccination antibody responses, have yet been done before, although scarcely [17]. A major difficulty, in modelling influenza vaccination out-

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comes, is how to identify health parameters, suitable for general use [9]. To deal with the complexity of this task, we reached out for the concept of a systems biology and machine learning methods, originally applied to analyse high-dimensional, non-linear data, provided by the sophisticated diagnostic methods, such as genomics and proteomics [18,19]. Based on this approach, we showed that it is possible to construct useful model of influenza vaccination outcome [20]. In this paper, we have further elaborated this work. By varying criteria for definition of the model's outcome measure (that is, low antibody response to influenza vaccination), we have showed that a set of health parameters, albeit limited, are necessary for model to achieve a wider practical use.

2. Methods

2.1. Population

The study was performed in a family practice, during the routine vaccination procedure against influenza, in the season 2003/2004. The sample was consisted of the kind of subjects who are commonly vaccinated against influenza in primary care, that is, those ones aged 50 years and more, and loaded with chronic medical conditions. A total number of 93 subjects, 35 male and 58 female, 50 - 89 years old (median 69), out of 150 of those vaccinated, gave their consent and were enrolled in the study. Study protocol was approved by the local ethics committee.

2.2. Influenza Vaccination

The commercially licensed trivalent inactivated split vaccine, recommended for vaccination that season, was used in the study, containing the following influenza virus strains: A/H_1N_1/New-Caledonia/20/99-like, A/H_3H_2/Moscow/10/99-like and B/ Hong Kong-330/2001-like.

Specific antibody production, to measure the vaccination outcomes, was determined by the standard method, Hemagglutination Inhibition (HI) test. At least a fourfold increase (≥4x) in antibody titre was used for expression of the specific antibody induction. The influenza B vaccine component was also tested on the B/Sicuan 379/99 strain, contained in the vaccine before the last content change, for a heterologous reaction (reaction on the component used for vaccination in the recent past) [21].

2.3. Systems Biology Methodology Approach

We have explored the possibilities of a systems biology methodology approach to identify health parameters appropriate for use in models of influenza vaccination outcomes. In contrast to the classical, reductionist approach, where only a few, already recognized variables can be evaluated, a systems biology is an analysis of how all components in a biological system are interconnected to produce a function, or a phenotype [18,19]. Since a large amount of poorly proved data enter the analysis, research can not be driven by the strongly defined hypothesis, but is rather based on the multi-step research protocol. Firstly, basic information is drown out from the publications. Based on these information, data is collected and integrated into the model, that is, mathematical description of the system. Advanced computer-based techniques, within the context of Artificial Intelligence, are eligible for this purpose. The final aim of the protocol is however, to develop a statistically significant model that can accurately predict responses (outcomes) to changes within the system [18,19].

2.4. A Database

After taking a closer look on the literature (MEDLINE/ PubMed and references screening), we could realised that many disease-related factors and age-related pathogenetic changes may alter the immune system functions. Based on these information, we collected a large number of a total of 52 parameters, to systematically, by many aspects, determine the health-status of examined patients (**Figure 1**).

Laboratory tests, to be chosen, had to meet two criteria: to determine the main age-related pathogenic changes, and to be available in the real health care system organisation. We performed blood tests indicating: 1) inflammation, 2) the nutritional status, 3) the metabolic status, 4) chronic renal impairment, 5) latent infections, 6) humoral immunity, and 7) the neuroendocrine status.

Performed laboratory tests:

- Inflammation: WBC* count, WBC differential (% neutrophils, lymphocytes, eosinophils, and monocytes), CRP, and serum proteins electrophoresis (a1, a2, b, g-globulins);
- Nutritional status: RBC count, haemoglobin, MCV, iron, serum albumin, folic acid, vitamin B12, and homocysteine;
- Metabolic status: fasting glucose, HbA1c, total cholesterol, HDL-cholesterol and triglycerides;

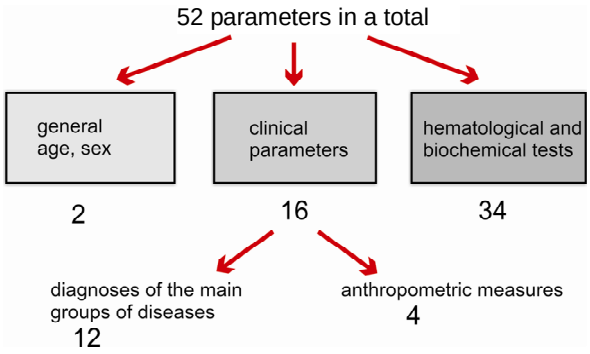

Figure 1. A database.

- Chronic renal impairment: Creatinine clearance;
- Latent infections: *Helicobacter pylori* specific IgA and IgG and cytomegalovirus specific IgG;
- Humoral immunity: IgE and A N A;
- Neuroendocrine status: Blood cortisol in the morning, TSH, fT3, fT4, and prolactin.

Abbreviations:

WBC (white blood cell); CRP (C-reactive protein); RBC (red blood cell); MCV (mean cell volume); HbA1c (glycosilated haemoglobin); HDL (high-density lipoprotein); ANA (antinuclear antibodies); TSH (thyroid-stimulating hormone); fT3 (free triiodothyronine); fT4 (free thyroxine).

Blood samples were collected from subjects two times prior the vaccination and once four weeks after the vaccination (to measure specific antibody induction). Haematological analyses were carried out on fresh blood samples, while sera for biochemical analyses and serological tests were separated by centrifugation and stored at –40˚C until assayed. Laboratory tests were performed by using standard techniques.

3. The Development of a Modelling Technique

In the first step of the analysis, we applied data mining algorithms, within machine learning methods, to the prepared database, in order to find meaningful patterns in the data [21]. Specifically, we used an in-house method, algorithms of the ILLM (Inductive Learning by Logic Minimization) system, originated in the Laboratory for Information Systems, Institute Rudjer Bošković, Zagreb, because of the availability and good classification properties of this method [22,23]. In this way, we in fact set up the functional relationship between a large, poorly identified input space and a specifically defined target outcome, allowing selection of the health parameters potentially relevant for the target outcome values (**Figure 2**).

Since influenza vaccines are trivalent, and factors related to past exposure to influenza viruses also affect vaccination outcomes, it is not possible to establish the unique equation to link the health-status of patients with low antibody response to influenza vaccination (used as the target attribute value). For this reason, four reasonable definitions of the target outcome values were set up, leading to the selection, from the input database, of the four sets of health parameters. In making definitions, an intention was to maximally exclude the influence of factors related to past exposure to influenza viruses, allowing health parameters to gain the full effect. Consequently, four recognizable patterns (clusters) in the data were identified, providing a relatively large pool of selected health parameters.

In the second step of the analysis, we constructed a definite model, with statistically significant properties [24]. The logistic regression (LR) with the forward selection procedure was used for this purpose, to determine the common impact of all three main factors, found as to have an impact on influenza vaccination outcomes, including: 1) factors related to past exposure to influenza viruses (the number of previous vaccinations, preexisted antibody titres and heterologous reaction, in this study indicated by the influenza virus strain B/Sicuan); 2) older age; and 3) the general health-status. Those health parameters previously selected by using data mining method, were included in the models. As the output, a binary variable was used, with one category (marked with 0) representing a patient who had a negative outcome, or low influenza vaccination response, and the other one (marked with 1) representing a patient with a positive outcome, or good influenza vaccination response. The selection criteria for the input variables was $p < 0.05$. By varying criteria for definition of the model's outcome measure (low antibody response to influenza vaccine), we have performed in a total four LR models. The SAS software is used to conduct the procedure, with standard overall fit measures such as likelihood ratio and score, as well as c statistics which measures discriminative power of logistic equation.

Criteria for definition of the LR models outcome measure (low antibody response to influenza vaccination):

- **Model No. 1** was based on the vaccine component B/Hong Kong, content of which has frequently been changed, and on which poor postvaccination antibody production was expected. The positive vaccination outcome value was defined as at least a fourfold (≥4x) increase in antibody titres, while the negative outcome value was defined as less than a fourfold (<4x) increase in antibody titres.

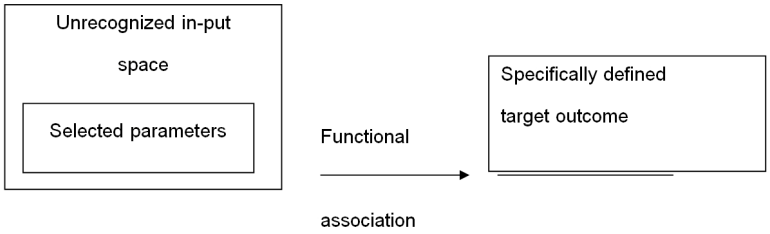

Figure 2. Parameters pre-selection based on using machine learning methods.

- **Model No. 2** was based on the vaccine component A/H1N1, characterised by the weak immunogenecity, on which also poor postvaccination antibody production was expected. The positive vaccination outcome value was considered as at least a fourfold (≥4x) increase in antibody titres, while the negative result of vaccination was considered as less than a fourfold (<4x) increase in antibody titres.
- **Model No. 3** was based on the same vaccine component as in the case mentioned above, however in the situation when the number of previous vaccinations was "zero", that is, in subjects receiving the vaccine for the first time. In this situation, even worse postvaccination antibody response on this vaccine strain, than in the case with the Model No. 2, was expected.
- **Model No. 4** was comprehensively defined, based on the results of HI-tests for all three influenza vaccine components (A/H1N1, A/H3N2 and B). As the criterion for definition of the negative (target) outcome value (low influenza vaccination response), at least a fourfold (≥4x) increase in antibody titres for one, or neither one vaccine component, was used. As the criterion for definition of the positive outcome value, at least a fourfold increase in antibody titres for two, or all three vaccine components, was used.

4. Results

4.1. Finding Patterns in the Data (Results of a Data Mining Method Application)

As the result of the repeated applications of data mining algorithms on the originally collected database, four recognizable patterns (clusters) in the data were identified (**Table 1**).

Specifically, no one diagnosis of the diseases was selected. Rather, there were all numerical parameters; except for age and triceps skinfold thickness, all others indicating haematological and biochemical disorders (**Table 1**). Based on the statistically significant properties of the parameters selected in the clusters, the best predictors of low influenza vaccination response were two pairs of parameters, including those indicating increased percent of monocytes and decreased percent of lymphocytes in WBC differential, and those indicating vitamin B_{12} deficiency and hyperhomocysteinemia (**Table 1**).

Due to parameters overlapping among the patterns, the number of selected parameters was further reduced, from 24 (6 in each cluster) to 16 different parameters, which are expected to deal with different real-life situations of vaccination (**Table 2**).

Those of selected parameters which overlap between two or more data mining models, are likely to indicate common intermediate mechanisms, linking chronic diseases with the immune system dysfunction (**Table 2**, the column on the right). Those ones, specifically selected in particular models, are likely to indicate specific, relatively well defined clinical conditions (clinical domains), associated with low influenza vaccination response (**Table 2**, the column on the left). These 16 selected health parameters were then used in the second-step analysis, as the input for the defined LR models (**Table 3**).

4.2. Models of Influenza Vaccination Outcomes with Statistically Significant Properties (Results of the Logistic Regression Analysis)

In the process of LR modelling, forward selection procedure was used for the reason to select the minimum number of input parameters, necessary for modelling. For all four defined situations of vaccination, statistically significant models with high predictive performances were obtained (**Table 4**).

Results of the LR analysis generally showed that parameters from all three proposed groups, including older age, parameters related to past exposure to influenza viruses, and those indicating the health-status disorders, are necessary for modelling (**Table 4**).

Results of the Model 3. showed that in some specific situations of vaccination, when poor postvaccination antibody production is expected, parameters indicating the health-status disorders might have greater impact on influenza vaccination outcome, then parameters indicating past exposure to influenza viruses (**Table 4**).

Based on performed LR models, several of the input health parameters, including FT4, HPA, GAMA, HOMCIS, LY and VITB12, were predominantly selected and are very likely to deal with most real-life situations of vaccination (**Table 4**).

5. Discussion

In this paper, the development of a modelling technique to predict potential outcome measures associated with influenza vaccination is presented.

Modelling response to influenza vaccination can improve our understanding of how previously yet proposed factors, older age, past influenza viruses exposure and health disorders, used together, affect antibody production after influenza vaccination. This may be useful when planning influenza vaccination protocols, to support decisions on target groups selection, as well as to facilitating further research. There is a general statement that the success of many preventive strategies could be improved and economically justified if relied on the possibility of identifying factors responsible for prediction of the outcomes and/or definition of the target groups [25]. The problem is that for many preventive tasks, risk and prediction factors have not yet been identified. A major difficulty, in modelling influenza vaccination outcomes, is

Table 1. Results of a data mining modelling. Four patterns of disorders.

Attribute ranking	Attribute	Cut-off value	Statistically significant properties	
			Sensitivity %	Specificity %
Model No. 1				
1.	Monocyte %	>8.0 (%)	90.0	70.8
2.	vitamin B_{12}	≤212.0 (pmol/L)	80.0	75.0
3.	homocysteine	>12.7 (mmol/L)	80.0	75.0
4.	fT_4	≤13.65 (pmol/L)	70.0	79.1
5.	Creatinine cl.*	≤1.55 (ml/s/1.73m^2)	70.0	75.0
6.	skinfold thickness	≥32.50 (mm)	80.0	62.5
Model No. 2				
1.	Monocyte %	>7.85 (%)	71.4	73.6
2.	g-globulins	>13.05 (g/L)	64.2	78.9
3.	MCV	>90.50 (fL)	78.5	63.1
4.	H.pylori IgA	>11.80 (IU/ml)	78.5	63.1
5.	prolactin	>90.24 (mIU/L)	85.7	57.8
6.	b-globulins	>8.50 (g/L)	64.2	73.6
Model No. 3				
1.	Lymphocyte %	≤35.10 (%)	65.6	63.6
2.	fT_4	≤13.65 (pm/L)	59.3	68.1
3.	Fasting glucose	≤5.45 (mol/L)	50.0	77.2
4.	b-globulins	≥8.05 (g/L)	53.1	72.7
5.	Monocyte %	>7.95 (%)	65.6	56.8
6.	Serum albumin	<45.35 (g/L)	75.0	54.54
Model No. 4				
1.	Lymphocyte %	≤ 35.40 (%)	56.7	89.4
2.	Monocyte %	>7.95 (%)	59.7	84.2
3.	Skinfold thickness	≤34.50 (mm)	65.6	73.6
4.	fT_4	≤14.5 (pmol/L)	71.6	63.1
5.	age	>65.5 (years)	71.6	63.1
6.	TSH	>1.39 (UI/ml)	59.7	68.4

*Abbreviations: fT_4 (free thyroxine); Creatinine cl. (Creatinine clearance); MCV (Mean Cell Volume); H. (Helicobacter) pylori; TSH (thyroid-stimulating hormone).

Table 2. A pool of 16 selected parameters.

Data Mining models	Parameters selected in a particular model	Parameters overlapping in 2 or more models
Model No. 1	Creatinine clearance, Homocysteine	Monocyte %, Vitamin B_{12}, fT_4, Triceps skinfold thickness
Model No. 2	*H. pylori* IgA*, *g*-globulins, Prolactin	Monocyte %, MCV [indicating vitamin B_{12}], *b*-globulins
Model No. 3	Fasting glucose, Serum albumin	Monocyte %, Lymphocyte %, fT_4, *b*-globulins
Model No. 4	Age, TSH	Monocyte %, Lymphocyte %, fT_4, Triceps skinfold thickness

*Abbreviations: H. (Helicobacter) pylori; fT4 (free thyroxine); MCV (Mean Cell Volume); TSH (thyroid-stimulating hormone).

the wide range of factors related to chronic aging diseases [9]. To overcome this difficulty, we suggest the use of a systems biology approach, considered as both, a step-wise research protocol and a systematic health parameters record [20]. The main strength of this approach is that by increasing the number of health parameters in the input, we in fact increase the chance of identifying those ones relevant for general use, in models of prediction, even if research is based on a single study and a small sample. In other words, by taking an automatic

Table 3. Input parameters for the defined LR models and their descriptive statistics.

Parameter no.	Parameter code	Parameter description	Descriptive statistics
1.	VACC*	A number of previous vaccinations 0 = vaccinated for the first time, previously vaccinated: 1 = once, 2 = two or three times, 3 = four or more times	0 = 39.79%; 1 = 20.43%; 2 = 13.98%; 3 = 25.81%
2.	H1N1_1	Pre-existed antibody titre on the influenza virus A/H1N1 strain	mean = 11.08; stdev = 22.38
3.	H3N2_1	Pre-existed antibody titre on the influenza virus A/H3N2 strain	mean = 69.68; stdev = 63.54
4.	KONG_1	Pre-existed antibody titre on the influenza virus B/Hong Kong strain	mean = 43.44; stdev = 99.90
5.	SICM_1	Pre-existed antibody titre on the influenza virus B/Sicuan strain	mean = 30.32; stdev = 44.64
6.	**GLU****	Fasting blood glucose	mean = 6.52; stdev = 2.10
7.	**SKINFOLD**	Triceps skinfold thickness (indicating malnutrition)	mean = 33.37; stdev = 7.38
8.	**AGE**	Age	mean = 67.66; stdev = 7.96
9.	**HPA**	*Helicobacter pylori* specific antibodies type IgA (indicating chronic gastritis)	mean = 32.61; stdev = 51.39
10.	**MO**	Monocytes % in White Blood Cell differential (indicating immune cells activation)	mean = 8.10; stdev = 2.26
11.	**LY**	Lymphocytes % in White Blood Cell differential (indicating lymphopenia)	mean = 35.45; stdev = 8.99
12.	**MCV**	Mean Cell Volume (indicating vitamin B12 deficiency)	mean = 91.03; stdev = 5.03
13.	**ALB**	Serum albumin (indicating inflammation/malnutrition)	mean = 46.11; stdev = 3.13
14.	**CRCLEA**	Creatinine clearance (indicating chronic renal impairment)	mean = 1.69; stdev = 0.45
15.	**HOMCYS**	amino acid homocysteine (indicating the nutritional status/chronic renal impairment)	mean = 12.35; stdev = 3.81
16.	**BETA**	beta-globulins in serum proteins electrophoresis (indicating low-grade chronic inflammation)	mean = 8.44; stdev = 0.94
17.	**GAMA**	gamma-globulins in serum proteins electrophoresis (indicating low-grade chronic inflammation/chronic humoral immunisation)	mean = 12.47; stdev = 2.29
18.	**VITB12**	Vitamin B12 (indicating vitamin B12 deficiency/the nutritional status)	mean = 284.33; stdev = 158.79
19.	**PRL**	Hormone prolactin (indicating hyperprolactinemia)	mean = 124.57; stdev = 120.39
20.	**TSH**	TSH (thyroid-stimulating hormone) (indicating thyroid gland hormone hypofunction)	mean = 2.04; stdev = 2.61
21.	**FT4**	Free thyroxine (thyroid gland hormone) (indicating thyroid gland hormone hypofunction)	mean = 14.01; stdev = 2.21
22.	Output	Vaccine response (0 = negative, less then fourfold increase in antibody titre) (1 = positive, fourfold and more increase in antibody titre)	

*Unbolded variables are related to past exposure to influenza viruses; **Bolded variables are related to the health-status disorders.

search across the large, unknown input space, it is as we take a shortened way, overcoming the need of performing multiple and larger studies (**Figure 2**). To ensure the accuracy of the results to be achieved, these selected health parameters are then used for building the models with the statistically significant properties, in our example provided in the form of the LR (**Table 4**).

This is the first attempt of this kind, to build models to predict responses to influenza vaccine, suitable for general use. The major concern might be on the generalizability of these results. This concern is due to the known fact that variation in local working environment and in characteristics of local population groups may influence the research results. Justification of these results may be found in the theoretical background a systems biology methodology approach arises from, assuming that the selected health parameters are reflective of their "natural clustering" (functional gathering) within the common biological networks, in this case linking chronic aging diseases burden with low antibody response to influenza vaccine [19]. Of course, future research, on other and larger samples, or by using vaccines with different component composition, will be needed to confirm whether these selected health parameters can be more generally used.

Our results showed that all three proposed groups of parameters, those related to previous influenza viruses exposure, those indicating the health-status disorders, as well as older age, participate in making up output values of performed LR models, thus providing an indirect proof that by using a systems biology approach it is possible to identify relevant health parameters and to build useful models of influenza vaccination outcomes (**Table 4**).

Table 4. Logistic regression results.

Attribute ranking	Attribute	Estimated parameter	p-value
	Model No. 1		
1.	**AGE**	0.0526	0.0013
2.	**KONG_1**	0.0843	0.0117
3.	**VACC (0)**	1.8036	0.0575
4.	**H1N1_1**	–0.0241	0.0721
5.	**VACC (1)**	2.0287	0.0382
6.	**SICM_1**	–0.0133	0.0976
Model quality: Likelihood ratio = 42.428 [p = 0.0001]; c = 0.863; Somers' D = 0.725; AIC = 128.142.			
	Model No.2		
1.	**HOMCYS**	0.1922	0.0132
2.	**FT4**	–0.1790	0.0992
3.	**H1N1_1**	0.0472	0.0892
4.	**VACC (1)**	1.1912	0.0871
5.	**VACC (2)**	1.4516	0.0633
Model quality: Likelihood ratio = 20.022 [p = 0.0012]; c = 0.764; Somers' D = 0.528; AIC = 124.156			
	Model No. 3		
1.	**HPA**	–0.0375	0.0268
2.	**FT4**	–0.6004	0.0314
3.	**VITB12**	–0.00632	0.0708
4.	**GAMA**	0.5176	0.0646
Model quality: Likelihood ratio = 20.945 [p = 0.0003]; c = 0.897; Somers' D = 0.794; AIC = 51.961			
	Model No. 4		
1.	**LY**	0.0759	0.0053
2.	**VACC (1)**	–1.7413	0.0118
3.	**VITB12**	0.00301	0.0095
4.	**SICM_1**	–0.0300	0.0400
5.	**FT4**	0.2290	0.0687
Model quality: Likelihood ratio =30.759 [p = 0.0001]; c = 0.834; Somers' D = 0.669; AIC = 123.263			

In addition, these results indicate that influenza vaccine components on which poor antibody responses are expected, are critical for modelling, as it is the case with the component A/H1N1, characterised with low immunogenecity and frequent absence of pre-existed antibody titres (**Table 4**, Model No. 1 and No. 2) [26]. Experiences gained until now in epidemiologic studies indicate that, in general, the worst postvaccination results can be expected on this vaccine component, in the elderly group lacking in pre-existing antibody titres, that is most commonly the case with those ones vaccinated for the first-time [26]. Based on our results, even in this extreme situation, it is possible to make prediction on influenza vaccination outcome. In this situation, parameters indicating the health-status disorders become critical for modelling (**Table 4**, Model No.3). Another critical point is the component B/H.Kong, the content of which has recently been changed and on which an unfavourable, heterologous reaction (in this study indicated by the influenza virus strain B/SICUAN), was expected (**Table 4**, Model No.1) [27].

As with respect to parameters indicating the health-status, our results indicate that a few although relevant health parameters, such as those indicating B-vitamins deficiency, hyperhomocysteinemia, relative lymphopenia, chronic humoral immunisation, thyroid gland hormone hypofunction and chronic gastritis caused by *Helicobacter pylori* infection, are sufficient to meet the needs for modelling, in a variety of real-life situations of vaccinations (**Table 4**). These parameters are likely to provide mechanisms to link chronic aging diseases with the immune system dysfunctions, while closer clinical contexts these parameters might be placed on are likely to be indicated by the results of data mining analysis, consistently with the parameters specifically selected in particular data mining models (**Table 2**). Based on comparison of the results of data mining analysis with the existing knowledge, it is likely that four chronic clinical conditions can contribute to low antibody response to influenza vaccination, including: 1.impaired renal function, especially syndrome characterized with hyperhomocysteinemia (Model No.1) [28,29], 2.chronic gastritis, caused by *Helicobacter pylori* infection and accompanied by chronic humoral immunisation (Model No.2) [30], 3.impaired glucose metabolism, accompanied by protein malnutrition (Model No.3) [31], and 4.aging of the hypothalamus and the pituitary gland, accompanied by the neuroendocrine system dysfunction (model No.4) [32].

In favour of the meaning of our results, intermediate disorders, hyperhomocysteinemia and B-vitamins deficiency, have already been recognised as markers of impaired immunocompetent cells turn-over and of turning the bias of the immune reaction from specific to non-specific (in this study indicated by increased percent of monocytes and decreased percent of lymphocytes in WBC differential) and from cellular to humoral immune response (in this study indicated by chronic humoral immunisation) [28,29].

On-line health parameters record and computer program experts working as a part of medical teams will be needed to implement this approach in routine practice. We suggest here use of a systematic health data record based on simple, low-cost parameters collection, known

as to be available in primary health care, as an approach for the first step knowledge discovery on the issue. The reasoning is the recent adoption of the electronic health record in primary health care that is likely to provide a huge potential for parameters collection and integration.

In general, our results indicate that a critical set of health parameters are to be identified, to meet the needs of different situations of modelling (that is, of variation in definition of the model's outcome measure). The challenge will be to take some other considerations into account, e.g., sex (male vs. female), serum cytokine levels, such as TNF-a, IL-1, IL-6, or IL-5, weight, etc. We also propose this method could be applicable to other vaccinations and other therapeutics to have a more global approach.

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